The role of auto-antibodies in idiopathic inflammatory myopathies.

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Dubai, October 29th 2019

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Learning objectives

- **Auto-antibodies** and muscle biopsy are important in the diagnosis of IIM, with direct prognostic relevance and direct impact on therapeutic decisions, e.g.:
  - No therapy in sIBM
  - Search for tumour in DM, search for ILD in ASS, etc.

- Inflammatory myopathy can occur without the presence of inflammatory infiltrates in muscle tissue (NAM)
  - Role of myositis-specific antibodies
  - DD muscular dystrophy!
  - Treatment!

- Inflammatory infiltrates in muscle tissue are not necessarily due to myositis, but can occur in other (hereditary) muscle diseases (e.g. FSHD, LGMD R2: No treatment)
Heterogeneous group of rare autoimmune diseases affecting skeletal muscles

But also various other organs may be involved (skin, lung, heart, joints)

Classifications:

• Bohan and Peter (1975): PM and DM
• Griggs and Askanas (1991): IBM
• Love (1991): first attempt to classify myositis based on MSAs
• Troyanov (2004): novel serological classification of IIM myositis-specific antibodies (MSAs)
  incl. anti-synthetase syndrome (ASS)
• ENMC (2004): clinico-pathological criteria, necrotizing autoimmune myopathy (NAM)
• Pestronk criteria (2011): histopathological classification
• EULAR-ACR classification (2017)
- **Myositis-associated** antibodies (MAA): also in systemic diseases (CTD)
- **Myositis-specific** antibodies (MSA): specific for IIM

Ref: Betteridge and McHugh, J Internal Med 2016
Classification in 5 groups:

- Dermatomyositis
- Non-specific (‘overlap’) myositis
- Antisynthetase syndrome (ASS)
- Necrotising auto-immune myopathy (NAM)
- Inclusion body myositis (IBM)
Importance of classifying IIM:

- Distinct diseases
- Distinct pathomechanisms
- Different risks of associated cancer
- Different comorbidities
- Different responses to immunosuppressive treatment
- Different prognosis
- Improving stratification in clinical trials
- Facilitating diagnosis in atypical cases
Dermatomyositis: Summary

• Adults (DM), children (JDM); F > M
• Subacute onset (weeks to months)
• Symmetrical and proximal muscle weakness ± myalgia

• Involvement of other organs possible:
  Skin changes
  Interstitial lung disease (ILD)
  Pericarditis
  Dysphagia

• Serum-CK: 1-50N
• Presence of MSAs (TIF1γ, NXP2, Mi2, SAE1, MDA5): 50-80%
• Association with malignancy possible
  (DM 6-45%; TIF1γ, NXP2)

• Treatment: steroids, immunosuppressive therapy
Necrotizing auto-immune myopathy: summary

- NAM, also: immune-mediated necrotizing myopathy (IMNM)
- 20% of IIM
- Antibodies against:
  - **SRP** = signal recognition particle
  - **HMGCR** = 3-hydroxy-3-methylglutaryl-coenzyme-A-reductase (65% use of statins)
  - 30-40%: AB not known
Subacute progressive symmetrical proximal muscle weakness ± myalgia
Dysphagia, ILD (SRP), cardiac (SRP)
Association with malignancy possible (SRP 5%)
Very high serum-CK (3000-25000 U/l)
Muscle biopsy: necrosis, no inflammatory infiltrates!
DD rhabdomyolysis, hereditary muscular dystrophies, toxic myopathies!
Immunosuppressive therapy (often resistant)
Antisynthetase syndrome (ASS): summary

• Antibodies against aminoacyl-tRNA-synthetases:
  25-30 % of IIM
  **Jo1** (histidyl), PL-7, PL-12, EJ, OJ, KS, Zo, Ha

• **Clinical** presentation ASS:
  ◊ Myositis
  ◊ Non-erosive arthritis
  ◊ Mechanic’s hands
  ◊ Interstitial longfibrosis (ILD); 70-89% (anti-Jo1)
  ◊ Cardiac involvement
  ◊ Raynaud phenomenon
  ◊ Fever, weight loss

• Association with malignancy possible (Jo1: 12%)
• Immunosuppressive **therapy** (often resistant)
Inclusion body myositis (IBM): summary

- Onset mainly > 50 y; M >> F
- Chronic progressive weakness of quadriceps, finger flexors, foot dorsiflexors
- Often asymmetrical
- Dysphagia (>>>)

- Serum-CK: 1-12N
- Presence of NT5C1A-antibodies in 34%
- No association with cardiac involvement or ILD
- No association with malignancy

- NO treatment!
Treatment of IIM (except IBM): Overview

1st Line Therapy
- Steroids: Prednisolone 1mg/kg/day PO for 4-6 weeks then slow taper
- Severe cases: IV Methylprednisolone 1g/d for 3 days followed by oral prednisolone

Steroid-sparing agent
- MTX or AZA or MMF
- Tacrolimus/cyclosporin in cases with associated ILD

If treatment resistant: Re-visit diagnosis and confirm IMIM

2nd Line Therapy
- Add-on Options
  - Consider dual immunosuppressive therapy or
  - IV Immunoglobulin (especially for DM and NAM) or
  - Rituximab (especially for DM and NAM)

3rd Line Therapy
- Biological Therapies
  - B/T-cell therapies
  - Anti-cytokine therapies

Ref: Needham and Mastaglia, Neurotherapeutics 2016
Differential diagnoses of IIM

- Vascularitis, CTD
- Viral/bacterial/fungal myositis
- Granulomatous myositis
- Polymyalgia rheumatica
- Limb-girdle muscular dystrophies (LGMD)
- Facio-Scapulo-Humeral muscular dystrophy (FSHD)
- Toxic myopathies
- Metabolic / Mitochondrial myopathies
- Myofibrillar myopathies, hereditary IBM (GNE, VCP)
- ...
References

- Neuromuscular homepage: https://neuromuscular.wustl.edu/